Remarks

This paper responds to the Office action in this patent application mailed July 23, 2002. With this amendment, claims 66-71 and 97 are pending. Claims 55-59 and 96 have been canceled. Reconsideration of the present application is respectfully requested in view of the present amendments and remarks.

The applicants petition the Commissioner for a one-month extension of time in which to file this amendment. A separate petition for an extension of time is enclosed.

Attached hereto is a marked-up version of the changes made to the title by the current amendment. The attached pages are captioned **"Version with markings to show changes made."**

I. Amendments

Claims 55-59 and 96 have been cancelled in accordance with Applicant's election of the claims of Group II for prosecution in the present case.

The title of the application has been amended to clearly indicate that the claims of the present invention are directed to antiviral methods using ovine interferon-tau as required by the Examiner.

No new matter has been made by the amendments.

II. Restriction requirement

On April 22, 2002, in response to a restriction requirement imposed by the Examiner on March 21, 2002, Applicant elected the claims of Group II, directed to methods of inhibiting viral replication, with traverse, for examination in the present case. In the present Office action, the Office has made the restriction final.

Applicant hereby confirms the election of Group II. Non-elected claims 55-59 and 96 have been canceled by this amendment.

However, Applicant intends to petition the Commissioner under 37 C.F.R. § 1.144 to review the restriction requirement with regard to the election of a single peptide sequence from sequences identified as SEQ ID NOS: 2, 5, 6, 7, 8, 9 and 10. Applicant

elects to defer the filing of a petition under 37 CFR § 1.144 until after final action or allowance of the pending claims.

III. Rejection under 35 U.S.C. § 112, second paragraph

Claims 66 and 97 were rejected under Section 112, second paragraph, as allegedly indefinite for failing to particularly point out and claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

The Examiner asserts that recitation of the phrase "at least about" in claims 66 and 97 is vague and indefinite since it makes the dosage rather imprecise. The Examiner relies on *Amgen v. Chugai Pharmaceutical Co.* (927 F.2d 1200, 18 USPQ2d 1016 (Fed.Cir. 1991)) where, because there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity was covered by the term "about", the Court found the term indefinite. Applicant disagrees and submits that the present facts distinguish from *Amgen* for the following reasons.

Whether or not a claim complies with §112, second paragraph's requirement to distinctly claim the subject matter requires a determination whether one of skill in the art would understand what is claimed when read in light of the specification. *Amgen v. Chugai Pharmaceutical Co.*, 18 USPQ2nd 1016 at 1030 citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.* 225 USPQ 634 (Fed. Cir. 1985). Present claims 66 and 97 recite an INFτ dosage of "at least about" $5x10^4$ units/day for inhibiting viral replication. The specification on page 58, line 4, teaches that "IFNτ can be administered at rates from about $5x10^4$ to 20 $x10^6$ units/day to about $500x10^6$ units/day or more." Thus, the specification provides an explicit teaching of a suitable dosage range for IFNτ. Given this, a skilled artisan would understand the dosage range of ovine interferon-τ being covered in the methods of claims 66 and 97.

The explicit teaching in the present specification of a suitable dosage range distinguishes Applicant's use of the phrase "at least about" from the facts in *Amgen*, on which the Examiner relies. In *Amgen*, patentee's claim to a specific activity for erythropoietin of "at least about" 160,000 was found indefinite for because, *inter alia*,

there was nothing in the specification that gave any indication as to what range of specific activity is covered by the term "about". Further, in *Amgen*, measurement of the specific activity was not possible with any degree of accuracy, *e.g.,* a range of error was inherent in measurement of specific activity. Furthermore, there was close prior art that cited a specific activity of erythropoietin of 128,620. The combination of these reasons led the court to find the phrase "at least about" indefinite as applied to those facts.

> Importantly, the court then stated:
> In arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as a ruling out any and all uses of this term in patent claims. It may be acceptable in appropriate fact situations. *Amgen 18 USPQ2d 1016 at 1031.*

Since the present facts distinguish from *Amgen* the Examiner's reliance on Amgen to find instant claims 66 and 97 indefinite is misplaced. Namely, the specification provides a explicit teaching of a suitable dosage range. Further, there is no issue, as there was in *Amgen,* of measuring with accuracy the specific activity of the claimed protein, since no similar measurement that has an "inherent degree of uncertainty" is involved in determining a dosage range.

Moreover, the term "about" has been found by the court to be definite, as set forth in M.P.E.P. §2173.05(b).

Accordingly, for all these reasons, Applicant submits that the phrase "at least about" in claims 66 and 97 satisfies the definiteness requirement of 35 U.S.C. §112, second paragraph, since a skilled in the art would understand the dosage range of ovine interferon-τ being covered in light of the disclosure in the specification. Withdrawal of the rejection is respectfully requested.

IV. Rejection under 35 U.S.C. § 103(a)

Claims 66-71 and 97 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Imakawa *et al.* (1987a; *Nature* 330:377-379) in view of Imakawa *et*

al. (1987b; *J. Cell. Biol.* 105(4 part 2):11A, abstr. 49), and Cummins (U.S. Patent 5,019,382). Applicant respectfully traverses this rejection for the following reasons.

A. The Invention

The present invention, as embodied in claim 66, is directed to a method of inhibiting viral replication, comprising contacting cells infected with a virus with ovine interferon-tau at a dosage of at least about 5×10^4 units/day to inhibit viral replication within the cells.

An advantage of the present invention is that interferon-tau exhibits potent antiviral activity with limited cytotoxic effects, as compared to interferon-alpha or interferon-beta. This advantage enhances the therapeutic window available for interferon-tau as a treatment, permitting higher doses and/or prolonged duration of treatment not feasible with interferon-alpha or interferon-beta due to the high cytotoxicity prevalent in alpha- and beta- interferon treatments.

B. The Cited Art

1. Imakawa (1987a) teaches the nucleotide and deduced amino acid sequence of ovine trophoblast protein-1 (oTP-1), an embryonic secretory protein synthesized by sheep conceptuses and targeted in a paracrine manner to the uterine epithelium of the mother, and implicated in signaling maternal recognition in pregnancy. The deduced amino acid sequence shows similarity to a range of mammalian alpha-interferons. Imakawa suggests that oTP-1 and its isoforms might represent interferons of highly specialized function.

Imakawa (1987a) does not disclose oTP-1 (ovine interferon-tau) as exhibiting antiviral properties, oTP-1 dosage ranges, and does not disclose or suggest treating a cell with oTP-1 to inhibit viral replication in such cell. Further, the reference provides no suggestion as to the advantage of the reduced cytoxicity of interferon-tau as compared to interferon-alpha in inhibiting viral replication in a cell.

2. Imakawa (1987b) discloses in a meeting abstract that oTP-1 has "antiviral and antiproliferative properties of an interferon". There is no data provided to support this statement.

As with the first Imakawa reference, this reference provides no suggestion of suitable dosage ranges for oTP-1, nor does it disclose or suggest the advantage of the reduced cytoxicity of interferon-tau as compared to interferon-alpha in inhibiting viral replication in a cell.

3. Cummins teaches the use of human alpha-interferon for treating immuno-resistant diseases. Cummins teaches nothing about interferon-tau, the antiviral properties of interferon-tau, effective dosages of interferon-tau, or the use of interferon-tau to inhibit viral replication in cells. In particular, the reference provides no suggestion as to the advantage of the reduced toxicity of interferon-tau as compared to interferon-alpha in inhibiting the growth of tumor cells in a subject.

C. Analysis

As noted above, none of the cited references, either singly or in combination, show or suggest the possibility of using ovine interferon-tau at dosages of at least about $5x10^4$ Units/day to inhibit viral replication in cells infected with a virus.

The Examiner asserts that it would have been obvious to a skilled artisan to treat cells infected with a virus with oTP-1 because Imakawa (1987a) teaches that oTP-1 has structural properties of an alpha-interferon; Cummins teaches that viral infections can be effectively treated; and Imakawa (1987b) teaches that the antiviral properties of oTP-1 have been confirmed experimentally. Applicant submits that the Examiner's assertion relies on improper assumptions and overlooks the claimed dosage limitation.

First, the Examiner's assertion that Imakawa (1987a) "teaches oTP-1 has structural properties of an alpha IFN", reaches beyond the statement in Imakawa (1987a) on the structural comparison of oTP-1 and alpha interferons. In fact, Imakawa (1987a) states on page 378, Col. 1, "[t]he primary amino-acid sequence inferred from this nucleotide sequence has a 45-55% sequence homology with....interferons of the

alpha family." Thus, the fact is that IFNτ exhibits limited homology with interferon alphas, as also set forth in Applicant's specification on page 8, lines 6-23. Applicant submits that substantially more than a limited homology of 45-55% is required to render interferon-tau "structurally similar" to interferon-alpha. Thus, the Examiner's reliance on Imakawa's purported teaching that interferon-tau and interferon-alpha are structurally similar is misplaced.

Second, with respect to the Examiner's reliance on Cummins's teaching that viral infections can be treated with interferons, the teaching of Cummins is limited to interferons alpha and beta. For the reasons given above, there is no basis for assuming that interferon tau acts like an interferon alpha. Because Cummins fails to disclose interferon-tau, the antiviral properties of interferon-tau, effective dosages of interferon-tau, or the use of interferon-tau to inhibit viral replication in cells and because there is no sound basis for analogizing interferon alpha and interferon tau, this assertion fails.

Moreover, even if there were some basis for drawing an analogy between interferon-tau and interferon-alpha, the Cummins teaching would direct a skilled artisan to dosages between about 0.1-5 IU/lb, which corresponds to about 15-750 IU for a 150 lb man. This dosage is about two orders of magnitude smaller than the presently clamed minimum dosage range. Nothing is Cummins suggests a dosage two orders of magnitude higher. In fact, it is clear that one would not contemplate a dosage two orders of magnitude higher for interferons other than interferon-tau, due to the known cytotoxicity of interferons alpha and beta. Cummins failure to teach a dosage range that is suitable for interferon-tau is evidence that it is improper to analogize the teaching for interferon alpha to interferon tau.

With respect to the statement in Imakawa (1987b) that oTP-1 has been shown to have antiviral properties, Applicant notes that there is nothing in Imakawa (1987b) that shows or suggests the claimed dosage range. All claim elements must be considered, and nothing in this reference or in the other cited teachings guides one of skill to a dosage of at least $5x10^4$ Units/day.

In fact, the Examiner states that dosages recited in the invention have not been taught by the art. The Examiner, however states that one skilled in the art, *knowing the*

similarity to other IFNs, would have tried various dosages to optimize the doses to inhibit viral replication. *See* Office action at page 5. This assertion is misplaced, since as discussed above there is no basis in the cited art for asserting interferon-tau is similar to other interferons. Moreover, the extreme discrepancy between the dosages for interferon alpha taught in Cummins and the claimed dosages suggests that selection of the dosage for interferon tau is not simply "routine optimization."

Even if selection of an effective interferon-tau dosage range were to be considered "routine optimization", M.P.E.P. § 2143.01 states that "[a] statement that modifications of the prior art to meet the claimed invention would have been ....'well within the ordinary skill of the art at the time the invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness". *See* M.P.E.P. § 2143.01 (original emphasis). As mentioned above, none of the cited references guide one of skill to the recited dosage of at least about $5x10^4$ Units/day. Nothing in the cited art establishes sufficient understanding within the knowledge of a skilled artisan that would have motivated the necessary modification in dosage to arrive at the claimed invention (see M.P.E.P. § 2143.01).

On a final note, Applicant notes that in obviousness determinations, it is the invention as a whole that must be considered. The invention as a whole embraces the structure, its properties, and the problem it solves. *In re Wright*, 848 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988). An analysis of obviousness must include consideration of the results achieved. *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990). As noted above, the present invention achieves more than is suggested by any of the cited references, namely the ability to inhibit viral replication in cells infected with a virus without the cytotoxicity of interferon-alpha, by administering to the subject an amount of ovine interferon-tau which exhibits a lower level of toxicity than would be shown by an equivalent amount of interferon-alpha.

Accordingly, for the reasons presented above, the method of claim 66 and the claims which depend from it are nonobvious. Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

V. Double Patenting Rejection

Claims 66-71 and 97 were rejected under the judicially created doctrine of obviousness-type double patenting at being unpatentable over claims 1-8 of U.S. Patent No. 5,942,223, issued August 24, 1999.

As the Examiner noted in the Office action (page 6, first full paragraph), the timely filing of a terminal disclaimer under 37 CFR 1.321(c) may be used to overcome a rejection based on a nonstatutory double patenting ground provided that the conflicting patent is shown to be commonly owned with the present application.

The present application and cited U.S. Patent No. 5,942,223 are assigned to University of Florida and thus, are commonly owned as required by 37 CFR 1.321(c). Enclosed is a terminal disclaimer under 37 CFR 1.321(c) disclaiming the terminal part of the statutory term of any patent granted on the present application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 5,942,223, issued August 24, 1999.

Withdrawal of the rejection is respectfully requested.

VI. Conclusion

In view of the above amendments and remarks, Applicant submits that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4309.

Respectfully submitted,
Perkins Coie LLP

Date: 11/25/2002

Karen Y. Hui
Registration No. 44,785

Correspondence Address:
Customer No. 22918

Appl. No. 09/746,919

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the title:

Antiviral Therapy Using Ovine Interferon Tau[Compositions and Methods of Use]